Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

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Allergy

REVIEW ARTICLE

Pediatric and adult eosinophilic esophagitis: similarities and differences

A. Straumann[1], S. S. Aceves[2], C. Blanchard[3], M. H. Collins[4], G. T. Furuta[5,6], I. Hirano[7], A. M. Schoepfer[8], D. Simon[9] & H.-U. Simon[10]

[1]Department of Gastroenterology, University Hospital Basel, Basel, Switzerland; [2]Division of Allergy and Immunology, Rady Children's Hospital, University of California, San Diego, San Diego, CA, USA; [3]Nestlé Research Center, Lausanne,Switzerland; [4]Division of Pathology and Laboratory Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [5]Gastrointestinal Eosinophilic Diseases Program, Children's Hospital Colorado, Digestive Health Institute, University of Colorado Denver School of Medicine, Aurora, CO, USA; [6]National Jewish Health, Denver, CO, USA; [7]Northwestern University School of Medicine, Chicago, IL, USA; [8]Department of Gastroenterology and Hepatology, University Hospital Lausanne, Lausanne, Switzerland; [9]Department of Dermatology, University Hospital Bern, Bern, Switzerland; [10]Institute of Pharmacology, University of Bern, Bern, Switzerland

To cite this article: Straumann A, Aceves SS, Blanchard C, Collins MH, Furuta GT, Hirano I, Schoepfer AM, Simon D, Simon H-U. Pediatric and adult eosinophilic esophagitis: similarities and differences. *Allergy* 2012; **67**: 477–490.

Keywords
corticosteroids; diet; dysphagia; eosinophilic esophagitis; Th2-type inflammation.

Correspondence
Prof. Alex Straumann, Chairman
Swiss EoE Research Group, Roemerstrasse 7, 4600 Olten, Switzerland.
Tel.: +41 62 212 55 77
Fax: +41 62 212 55 64
E-mail: alex.straumann@hin.ch

Accepted for publication 27 December 2011

DOI:10.1111/j.1398-9995.2012.02787.x

Edited by: Antonella Muraro

Abstract

Early in the 1990s, several case series described adults suffering from dysphagia and children with refractory reflux symptoms, both accompanied by an eosinophil-predominant infiltration, thereby conclusively distinguishing it from gastroesophageal reflux disease. Eosinophilic esophagitis (EoE) was recognized as its own entity in the adult and in the pediatric literature. In the last decade, evidence has accumulated that EoE represents a T-helper (Th)2-type inflammatory disease. Remodeling of the esophagus is a hallmark of EoE, leading to esophageal dysfunction and bolus impaction. Familial occurrence and disease association with single-nucleotide polymorphisms underscore the influence of genetics in this disease. Eosinophilic esophagitis may affect individuals at any age, although the clinical presentation is highly age dependent. There is a significant allergic bias in the EoE population, with the majority of patients having concurrent allergic rhinitis, asthma, eczema, and/or a history of atopy. One noteworthy difference is that in children, EoE seems to be primarily a food antigen–driven disease, whereas in adults, mainly aeroallergen sensitization has been observed. Treatment modalities for EoE include the 3Ds: drugs, diet, and dilation. The crucial question of whether adult and pediatric EoE are different phenotypes of one single entity or whether we are confronted with two different diseases is still open. Here, we review similarities and differences between EoE in adults and children.

History and epidemiology of adult and pediatric EoE

The esophagus is frequently affected by disturbances mainly because of the dysfunction of the lower esophageal sphincter, which is responsible for maintaining a large pH gradient. The history of adult and pediatric esophageal diseases is therefore strongly dominated by dysfunction of the esophago-gastric junction leading to gastroesophageal reflux disease (GERD) and its sequela. First in the 1980s, several studies identified eosinophilic infiltration of the esophagus, a tissue normally devoid of these cells (1). This finding was falsely interpreted as a histologic manifestation of GERD (2).

In the early 1990s, two case series described *adult patients* suffering from *dysphagia* associated histologically with an eosinophil-predominant infiltration. This pattern was immediately recognized as being different from GERD and was therefore labeled primary or idiopathic eosinophilic esophagitis (EoE) (3, 4). The presentation of dysphagia and food impaction in atopic individuals with endoscopic findings of esophageal rings and longitudinal furrows was distinct from the heartburn, regurgitation, and erosive esophagitis in GERD. A few months later, Kelly and colleagues reported on a series of allergic *children* suffering from severe *GERD-like symptoms refractory* to medical or surgery therapy. These

pediatric patients again had a relevant infiltration of the esophagus with eosinophils and responded to treatment with a hypo-allergic diet (5). Further studies demonstrated that these two different clinical presentations were probably two sides of the same coin, a clinicopathological disease later termed EoE. Below, unless otherwise indicated, statements refer – and are applicable – to both the pediatric and adult populations.

Originally, EoE was considered rather a rare curiosity than an epidemiologically relevant disease (6). However, in recent years, western gastroenterologists observed a dramatic increase in the number of newly diagnosed EoE cases (7–9). This observation raised the question whether the incidence of EoE has been truly increasing or whether the disease is more frequently as a consequence of heightened awareness by healthcare providers. Results from a recently published population-based long-term study suggest that the accelerated EoE incidence represents, in fact, a true increase (10).

Clinical characteristics of adult and pediatric EoE

While EoE may affect individuals at any age (11), clinical presentation is highly dependent on the patient's abilities to report symptoms associated with esophageal dysfunction (12). Recognition of clinical signs, along with laboratory and endoscopic findings, is critical for the identification of new patients with EoE and those with established disease and uncontrolled inflammation.

Medical history

Both children and adults with EoE are typically individuals in a good general condition. They present with unspecific symptoms, a variety of compensatory behavior strategies, or episodes of food impaction. Therefore, in adults and adolescents, it usually lasts 4–5 years before the EoE diagnosis is made (7, 8). Important clues to the diagnosis of EoE can be obtained by taking a careful patient's history that focuses on esophageal and upper abdominal symptoms.

Children report a wide range of symptoms, which are largely age dependent (Table 1). For instance, infants often present with *irritability*, *feeding problems, vomiting, and abdominal pain,* whereas older children, like adults, present with *dysphagia, heartburn*, or spontaneous *food impaction*. When symptoms do not respond to medical or surgical treatments for GERD, EoE should be strongly considered (5). Over time, children may develop *coping strategies* to avoid symptoms; when asked whether swallowing is problematic, they may respond 'no' but when further questions are posed, such as 'Do you wash food down with liquid? Are you the last one to leave the table? Do you chew your food for a long time? or Do you avoid foods such as meats or breads?' the answer is frequently 'yes', thereby indicating the development of compensatory behavioral strategies.

Eosinophilic esophagitis in adolescents and adults causes a rather narrow spectrum of symptoms; typically, they complain of *dysphagia for solids* (3, 4) (Table 1). Symptoms are more prominent and swallowing disturbances more pronounced when the ingested food's consistency is dry or rough and/or when patients eat too fast. During the disease course, more than one-third of untreated EoE patients will experience long-lasting *food impactions* that require endoscopic bolus removal (13). Eosinophilic esophagitis is the main cause of food impaction in young male patients. A minority of patients experience *retrosternal pain* that occurs either spontaneously, which is induced by ingesting alcohol (e.g., white wine) or acidic liquids (e.g., orange juice).

Table 1 Symptoms reported by pediatric and adult patients with eosinophilic esophagitis

Children	Abdominal pain
	Chest pain or heartburn
	Coughing
	Decreased appetite
	Dysphagia (food sticking – especially meat, bread, pasta, and pills; 'toy car' in throat; 'furball' in throat; sticky saliva; throat makes a clunking sound; food wads up; holds food in mouth for 15 min before swallowing; chews food finely; needs a much water to wash food down; and last one to leave the table)
	Food refusal (spits out food; throws food away; self-limits food; fear of choking; and picky eater)
	Choking/gagging
	Nausea
	Regurgitation
	Sleeping difficulty
	Throat pain (itchy, scratchy, spicy, and hot spit)
Adults	Dysphagia
	Food impaction
	Retrosternal pain

Adapted from Newton et al. (107).

Physical examination

In part, owing to the anatomic location of the esophagus hidden deep within the chest cavity, the physical examination of children and adults with EoE is typically normal (7, 8). In some children, failure to thrive may be obvious (7, 8). Features of concomitant allergic diseases (asthma, eczema, allergic rhinitis, etc.) are frequently found.

Laboratory analyses

Mild peripheral eosinophilia occurs in 5–50% of children and adults with EoE (3, 4, 7, 8). Approximately 70% of patients with EoE have elevated total IgE values (3, 4, 7, 8).

Endoscopic features

Upper endoscopy is the first diagnostic step in the work-up of individuals with dysphagia (14). Although there is neither a pathognomonic endoscopic sign nor a typical pattern of abnormalities, a considerable number of endoscopic features may be observed (Fig. 1). These signs usually appear in random combination and represent evidence of active

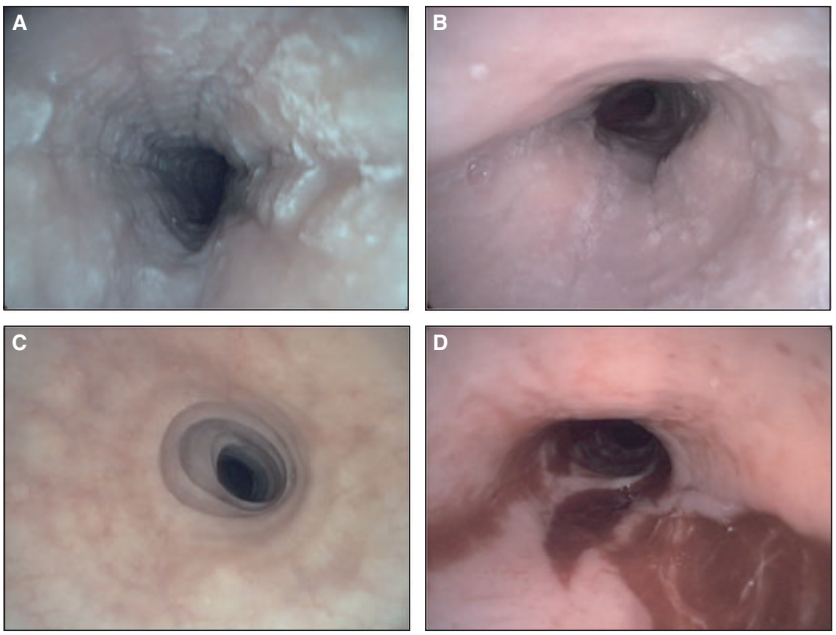

Figure 1 Endoscopic pictures illustrating the major endoscopic signs of eosinophilic esophagitis. (A) represents an acute and severe inflamed esophagus, whereas (B) shows an acute but only moderate inflamed organ. White exudates, furrowing, and edema with the loss of vascular visibility are the leading signs of inflammation. C and D illustrate signs associated with remodeling, such as fixed esophageal rings (=trachealization or corrugated rings) and crêpe-paper esophagus with deep laceration after minimal trauma. All four pictures are from adult patients.

inflammation with mucosal edema (furrows, exudates, etc.) or chronic inflammation with tissue remodeling (crêpe-paper mucosa, corrugated rings, stricture) (7, 8). To date, no systematic studies have compared endoscopic features of EoE in children and adults. But according to our clinical experience, signs of active inflammation occur mainly in children, whereas manifestations of chronic inflammation are observed more frequently in adults. The suspected diagnosis of EoE requires histologic confirmation with a mucosal biopsy (7).

Histopathologic features

Pathologic features of EoE are characteristic, but not specific because the etiology of the epithelial eosinophilic inflammation cannot be determined solely from microscopy. Pathologic features assessed using routine stains likewise do not distinguish biopsies taken from children from those of adults (Fig. 2).

Eosinophils

Eosinophils are not normally found in the esophageal epithelium (1), and the quantity of intraepithelial eosinophils is a crucial component in the diagnosis of EoE. The consensus recommendations, based on extensive literature review, endorse using the same minimum threshold level of esophageal epithelial eosinophilic inflammation for both children and adults (7, 8). Over time, in adults, intraepithelial eosinophils may diminish (15) but in children may increase (16). This apparent contradiction may be due to differing therapies, as well as to more skillful accommodation to disease (e.g., prolonged chewing) in adults compared with children.

Other inflammatory cells

Other inflammatory cells are also found in EoE biopsies. Reports that specifically state the quantities of those cells were surveyed (Table 2) (17–33) and several conclusions seem appropriate.

1 The method for reporting cell concentration varies widely, from peak number in one high-power field (hpf) to number per unit volume. Interstudy comparisons are very difficult with such diverse reporting variations. For clinical purposes, peak number per hpf is adequate; this number may be reported as peak count/unit area if the area of the hpf used for counting is known. Standardized reporting, for example, as peak number per unit area, would facilitate interstudy comparisons.
2 The quantities reported from stereology studies (reported as *thousands* of cells per unit volume) (20, 24) are considerably larger than from studies using other methods and suggest that inflammatory cell density in biopsies from adults is significantly greater than in biopsies from children. Similar stereology studies on biopsies from children should be performed to confirm or refute possible differences.
3 Few EoE studies include GERD as a reference group. Comparisons of inflammatory cells other than eosinophils

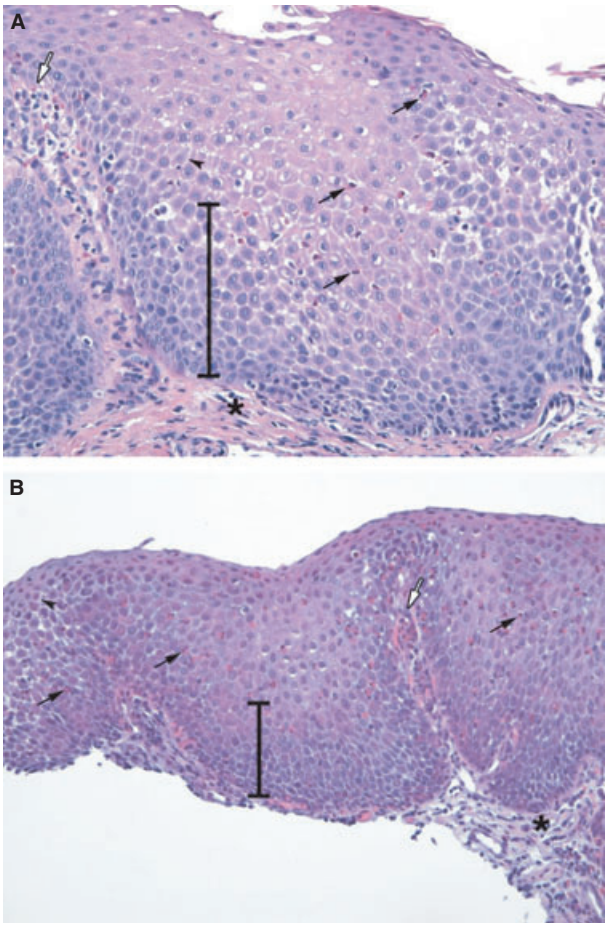

Figure 2 Biopsies from a child (A) and an adult (B) who have eosinophilic esophagitis show similar features. In each picture, black arrows point to numerous intraepithelial eosinophils in esophageal squamous epithelium, the black arrowhead points to dilated intercellular spaces, the black bar demarcates basal layer expansion, the white arrow points to the top of an elongated papilla, and although only scant amounts of lamina propria are attached, the asterisk rests on thickened collagen fibers. Original magnification ×200.

that may be important in pathogenesis or disease modulation are required to further explore similarities and differences between EoE and GERD. Equally important would be studies that include significant numbers of biopsies from patients who have proton pump inhibitors (PPI)-responsive esophageal eosinophilic inflammation (8).

4 Most studies report on either adults or children. In one study of both adults and children with EoE, CD3+ T cells were reported as 60.1 ± 11.09 (mean of 5 hpf) (range 18–105) (31), which is higher than reported solely for children (17, 18). In another study of both children and adults with EoE, maximum mast cell density (obtained from examination of 5 hpf) was 162 ± 87/mm^2 (range: 10–448), roughly comparable to another report of adults only (19, 32). Ideally, studies of biopsies from both children and adults should include subgroup analyses of children *vs* adults to minimize the possibility that any differences are because of different methods of quantification.

5 Inflammatory cells are increased in EoE compared with normal biopsies or biopsies from patients who have GERD. T-regulatory cells, however, although absolutely increased in pediatric EoE (17), might be relatively lacking, at least in adults with EoE (33).

Immunopathogenesis

The striking eosinophil infiltration of the esophageal tissue suggested that an immunologic mechanism contributed to the pathogenesis of EoE. The recognition that EoE represents a Th2-type inflammatory disease was a large stepforward in our understanding of the disease (19). This landmark study showed that the esophageal epithelium of patients with EoE contains not only eosinophils, but also IL-5-expressing T cells, B cells, and IgE-bearing mast cells, pointing to the possibility that EoE is an allergic entity (Table 2) (19). This same study also demonstrated that the inflammatory response in patients with EoE is restricted to the esophagus and does not involve stomach and/or duodenum (19). The Th2-type inflammatory profile of EoE was subsequently confirmed in pediatric and adult EoE (34), and relevant allergens were identified for both pediatric and adult EoE (see below). Moreover, a strong link between atopy and EoE was subsequently described in both pediatric and adult EoE patient groups (35, 36). It should be noted, however, that intrinsic (non-IgE mediated) forms exist in both pediatric and adult EoE in which no relevant allergens can be identified, neither by measuring IgE nor by performing skin prick or patch tests.

Increased numbers of dendritic cells and IgE-secreting plasma cells have also been described in the esophageal epithelium of patients with EoE (24). Besides the infiltrating leukocytes, the esophageal epithelial cells appear to contribute to the inflammatory response. For instance, the epithelial cells highly express TNF-α (19) and eotaxin-3 (25) that likely represent key factors largely responsible for the recruitment of eosinophils to the esophagus. Moreover, esophageal epithelial cells of patients with EoE have been reported to produce thymic stromal lymphopoietin (TSLP) (37), a cytokine favoring Th2 differentiation (38). Recent studies point to the possibility that the role of regulatory T cells may differ between pediatric and adult EoE. While increased numbers of regulatory T cells were seen in pediatric cases (38), adult patients with EoE were found to have a relative lack of FoxP3-positive T cells (33). Taken together, although the allergenic triggers partially differ (see below) and other reported minor differences may exist between pediatric and adult EoE, the main allergen-induced immunologic mechanisms leading to eosinophilic inflammation and allergen-specific IgE synthesis do not seem to be age dependent and appear to be very similar to other allergic diseases (Fig. 3).

The correlative studies in patients with EoE were largely confirmed by mechanistic studies performed in experimental mouse models of EoE. For instance, T-cell-deficient, but not

Table 2 Inflammatory cells in healthy individuals, patients with gastro-esophageal reflux disease, and patients with EoE

Quantification method	Normal		GERD		EoE		References
	Pediatric	Adult	Pediatric	Adult	Pediatric	Adult	
T cells							
CD3+							
Mean/3hpf	1 ± 1.4		0.67 ± 0.82		7.4 ± 6.33		(17)
Mean/5hpf	5.5 ± 2.3				28.2 ± 4.5		(18)
Mean/mm^2		180 ± 22.2				555 ± 54.6	(19)
Thousands/mm^3		15.9 ± 6.3				111.3 ± 28.7	(20)
Mean/hpf		14.0 ± 5.5				28.9 ± 11.9	(33)
CD4+							
Mean/all hpf	1.6 (0.4–2.5)†				3.6 (1.4–30.8)†		(22)
Thousands/mm^3		4.6 ± 2.8				27.4 ± 18.6	(20)
CD8+							
Mean/5hpf	5.9 ± 2.8				20.2 ± 8.1		(18)
Mean/10hpf					Distal: 36.2 ± 5.7 Proximal: 30.2 ± 5		(21)
Mean/all hpf	3.1 (1.8–4.4)†		13.2 (8.2–28.8)†		17.9 (6.8–24.1)†		(22)
Thousands/mm^3		11.3 ± 5.1				79.5 ± 23.4	(20)
FoxP3+							
Mean/all hpf	0.4 (0–1.2)†		4.7 (1.7–8.1)†		7.5 (3.6–13.8)†		(22)
CD3+/FoxP3+							
Mean/3hpf	1.6 ± 0.9		1.67 ± 2.07		10.7 ± 6.4		(17)
Mean/hpf		1.29 ± 0.68				1.65 ± 1.64	(33)
B cells							
CD20+							
Mean/mm^2	0.9 ± 1				12.4 ± 14.9		(23)
Mean/mm^2		0				7.4 ± 1.7	(19)
Thousands/mm^3		0		1.89 ± 3.47		2.48 ± 3.49	(24)
Mast cells							
Tryptase+							
Peak/hpf	4.6 ± 0.3				13.8 ± 6.76		(25)
Peak/hpf	3 (1–16)†		6 (3–11)†		20.5 (4–55)†		(26)
Mean/mm^2		4.0 ± 0.9				135 ± 17	(19)
Peak/hpf	0.5 ± 0.3				6.9 ± 1.4		(27)
Mean 3–5hpf	1 (0.3–4)†				23 (12–42)†		(28)
Mean/10hpf					Distal: 17.1 ± 3.5 Proximal: 7.3 ± 2.2		(21)
Mean/10hpf	0		7.8 ± 8.9		26.3 ± 12.7		(29)
Mean/3hpf				2.32 ± 4.24		9.51 ± 8.78	(30)
Thousands/mm^3		2.73 ± 3.68		10.63 ± 12.81		48.26 ± 40.03	(24)
Thousands/mm^3		6.9 ± 3.5				63.5 ± 37.9	(20)

EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease.
†Numbers in parentheses are interquartile ranges.

B-cell-deficient, mice seem to be unable to develop EoE (39). Moreover, experimental EoE was inducible by allergens (40) and IL-13 (41), and IL-5 and eotaxin were found to be crucial for disease development (41). Taken together, the data in experimental mouse systems support the view that EoE likely represents an allergic disease in which T cells and eosinophils play key pathogenic roles.

Remodeling of the esophagus is a hallmark of EoE, and both histologic and molecular features of this process have been described (42–45). Extracellular matrix proteins were found to be deposited in significant amounts in patients with EoE (42–44). Interestingly, the deposition of extracellular matrix proteins, including its associated subepithelial fibrosis, was reversible in EoE patients receiving topical corticosteroid therapy (42, 44). TGF-β1, a key cytokine for epithelial growth, fibrosis, and tissue remodeling, has been identified with EoE (42–44). Tissue remodeling suggests the existence of previous tissue damage. Indeed, TUNEL-positive epithelial cells indicative for cell death were particularly found in close proximity to eosinophil infiltrations (43), and tissue remodeling correlated with eosinophil degranulation (44).

The latter observations point to a possible role of the eosinophil in the immunopathology of the esophagus in patients with EoE. Immunohistochemical studies revealed

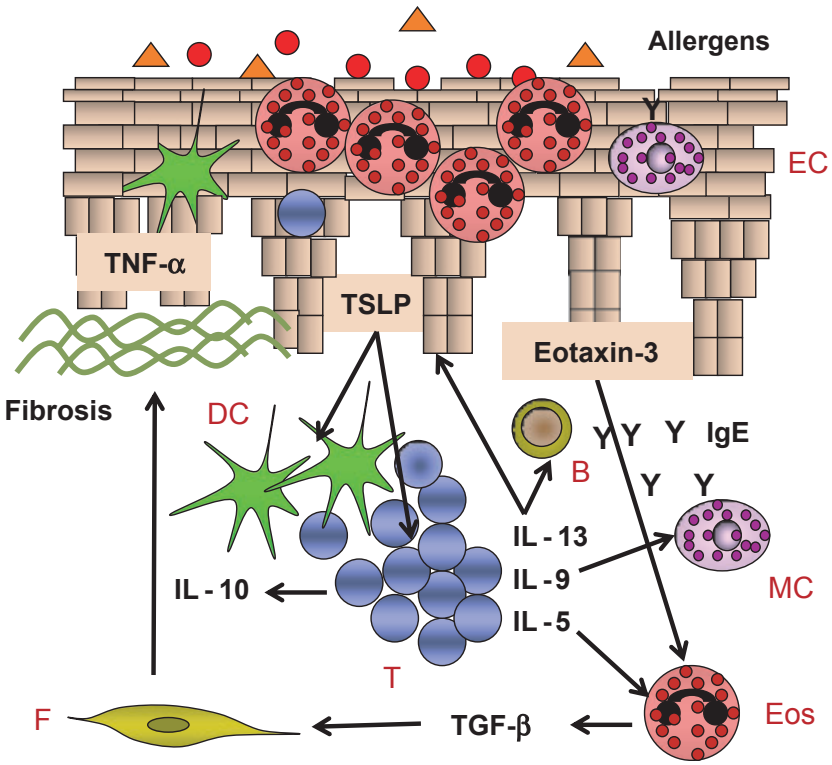

Figure 3 Simplified scheme on the immunopathogenesis of eosinophilic esophagitis (EoE). EoE is believed to be triggered by aero- and food allergens. The epithelial cells (EC) of the esophagus that are activated by IL-13 actively contribute to the inflammatory process. Thymic stromal lymphopoietin promotes dendritic cell (DC)-mediated Th2 differentiation, TNF-α increases adhesion molecules on endothelial cells (not shown), and eotaxin-3 attracts eosinophils (Eos). IL-13 helps B cells to produce IgE. IL-9 activates mast cells (MC), which bind IgE by their high-affinity IgE receptor. IL-5 activates eosinophils and may delay their apoptosis. There are also IL-10-generating T cells, which likely try to limit the inflammatory process. Eos and MC generate additional cytokines and participate in the immunoregulatory process (not shown). Eos also generates TGF-β, which stimulates fibroblasts (F) to produce extracellular matrix proteins. Eos may also damage epithelial cells by releasing cationic proteins and reactive oxygen species (not shown). It should be noted that mast cells and eosinophils generate additional inflammatory mediators that help in recruiting leukocytes (not shown), which subsequently migrate in the epithelial layer of the esophagus.

evidence for eosinophil degranulation in the esophageal epithelium (26, 43, 44). The granule proteins major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil peroxidase (EPO) have cytotoxic effects, explaining, at least partially, the death of epithelial cells associated with EoE. Eosinophil-mediated epithelial damage can also be explained by toxic hydrogen peroxide and halide acids generated by EPO, as well as reactive oxygen species (ROS) produced as a consequence of NADPH oxidase activation. Clearly, besides its role as an effector cells, eosinophils may contribute to EoE pathogenesis by their capacity to participate in immunoregulatory (46) and tissue remodeling processes (43). Whether eosinophils generate extracellular DNA traps (47–49) in patients with EoE remains an open question.

Allergic profile in adults and children with EoE

It has become increasingly clear that there is a significant allergic predisposition in the EoE population, with the majority of patients having concurrent allergic rhinitis, asthma, eczema, and/or a history of atopy (7). Based on its pathogenesis, it is likely that EoE represents a new manifestation of atopy. In *children*, EoE seems to be primarily a *food antigen–driven disease* with the majority of children responding to the elimination of common dietary antigens and having disease recrudescence upon reintroduction of the instigating food antigens (50–52). Also adult EoE may be driven by food antigens in many patients (53). Interestingly, in *adolescents* and *adults* with EoE, *aeroallergen sensitization* has mainly been observed (36, 54). However, these patterns of sensitization do not necessarily prove a shift in EoE triggers, but rather a shift in the known pattern of allergic sensitization in allergic subjects, consistent with a sensitization pattern that follows the atopic march (55).

Allergic diseases are found in the majority of patients with EoE (7, 8). While >50% of EoE subjects have a history of atopy, the diagnostic criteria and severity classifications for accompanying allergic disorders vary between reports. Nonetheless, approximately 40–75% of patients have allergic rhinitis, 14–70% have asthma (36, 56–59), and 4–60% have

eczema (36, 58, 60). Immediate hypersensitivity reactions to foods diagnosed using the recommended anaphylaxis guidelines (36) appear to be higher than in the general population and are reported to occur in as many as 24% of patients with EoE (54).

Aeroallergen and food sensitization in adult EoE

In adult patients, EoE is often associated with elevated serum IgE levels. Initial EoE reports mention elevated total IgE levels and concomitant allergic diseases in 70% and 77%, respectively (3, 4). A prospective study on 31 adult patients with EoE revealed specific IgE to aeroallergens, food allergens or both in 80%, and positive skin prick test (SPT) in 84% (36). In 63% of patients sensitized to food allergens, cross-reactive aeroallergens were identified, in particular, to grass pollen, wheat, and rye (36). However, elimination diet of wheat and rye failed to improve EoE symptoms in sensitized patients (60). Recent studies demonstrated sensitization to environmental allergens in 86–93% and to food allergens in 50–82% of adult patients with EoE (57, 61). Peanut, soybean, egg white, cow's milk, and tree nuts (62) as well as wheat, tomato, carrots, and onions (57) were identified as common food allergens in adult patients with EoE. Pan allergens present in pollen as well as in fruits and vegetables, for example, profilin, have been identified as relevant allergens in EoE (62). Because an elemental diet does not seem practical in adults, specific elimination diet can be tried.

Evidence that aeroallergen exposure could cause esophageal eosinophilia in adults comes from subjects with grass-induced allergic rhinitis and esophageal eosinophil infiltration during the grass pollen season (63). The role of aeroallergens in eliciting EoE has been shown in animal models using multiple aeroallergens, including *Aspergillus*, house dust mites, and cockroaches (40, 64). Interestingly, the onset of allergic airway diseases, reported by 68% of patients, preceded that of EoE (36). Seasonal exacerbations of EoE in spring and summer have been observed in a patient allergic to tree and grass pollen (65). Moreover, the number of newly diagnosed EoE peaks in spring, suggesting a potential role of aeroallergens (57, 66).

Aeroallergen and food sensitization in pediatric EoE

Similar to the adult data, pediatric patients commonly have aeroallergen sensitization and >70% have elevated total IgE. While a lack of elevated total IgE may indicate a subset of EoE children who do not have elevations in specific IgE to food or aeroallergens, the overall data do not support a need to follow or analyze total IgE levels in patients with EoE. Children are sensitized to both outdoor and indoor allergens, with reports of 26% and 37% of patients allergic to grass and *Alternaria*, respectively, and 16–19% sensitized to cockroach and house dust mite allergens (60, 64). Similar to adults, there can be seasonal variations in the diagnosis and severity of EoE in children (52, 67). Despite these clinical observations, a definitive instigating link between pollen and human pediatric EoE remains unclear. Therefore, further studies that clearly document the pattern of aeroallergen sensitization with the season of EoE onset and/or exacerbation are required.

In contrast to adults, the majority of children with EoE have food sensitization. Serum IgE detects more positive tests than does skin prick testing, but the clinical utility and significance of this increased detection is unclear. Currently, no published studies document a correlation of serum food-specific IgE levels with EoE instigation or propagation. In addition, there is a paucity of interventional data that use serum food-specific IgE as the basis for food elimination diets. In order to detect potential delayed-type food hypersensitivity reactions, atopy patch testing to foods has been instituted in EoE. The combination of food prick and patch testing has been reported to have high rates of success in predicting antigens that trigger EoE (52). While positive patch testing may aid in the creation of a directed elimination diet, standardization and validation of patch testing in EoE is still needed. Studies using prick, patch, and serum IgE testing for foods have found certain foods in common that are positive by all three test procedures in children, especially, milk, egg, and wheat (52, 59). Combined prick and patch testing additionally find corn, beef, chicken, barley, oat, and rice as common positive tests. Interestingly, an empiric elimination diet (milk, egg, soy, wheat, peanuts, tree nuts, fish, shellfish) followed by food reintroduction demonstrates that milk, wheat, egg, and soy are the four main EoE triggers in children (51). As such, future testing studies, including those that look for food-specific T cells (68), may do well to focus primarily on this specific subset of foods.

Genetics

Numerous studies have suggested EoE's strong genetic inheritability (12, 69). Indeed, 6.8% of patients with EoE have at least 1 family member suffering from the same disease (70), about three of four patients with EoE present with a family history of atopic disorders, three of four patients are men, 9 of 10 are Caucasian (70), and the sibling recurrence risk ratio is 80 in EoE, while it is approximately 2 for asthma (70–72). The two EoE subtypes, sporadic EoE and familial EoE, have been compared for clinical, endoscopic, pathological features, and global esophageal transcript expression profiles and were found to be very similar (70).

Because of our progress in understanding the immunopathogenesis of EoE, genes of proteins important for the immune responses were frequently the target of so-called candidate gene approaches. In one case-controlled study, a SNP in the 3′UTR (rs2302009, SNP+ 2496 T → G) of eotaxin-3 was identified as being associated with EoE (25). The *G* allele was over-represented and the *GG* genotype frequency was significantly higher in the EoE population. A family-based transmission disequilibrium test (TDT) confirmed that the allele *G* was preferentially transmitted by heterozygous parents to affected individuals. The association of this SNP with EoE was not dependent on the atopic status (25).

Moreover, in a pilot study, the frequency of the CC, CT, TT genotypes and the allele frequency of the C-509T SNP

(rs1800469) of TGF-α1 were analyzed in 20 patients with EoE. In this cohort, the CC genotype correlated with a responder status. Additionally, EoE patients with a CC genotype had significantly lower numbers of TGF-β_1-positive cells in the *lamina propria* than patients with a CT or TT genotype. This downregulation is probably due to the lack of YY-1 binding site in the C-bearing promoter that decreases TGF-B1 promoter activity and thus TGF-β1 expression (42).

Filaggrin downregulation has been associated with an impaired skin barrier function. Two loss-of-function genetic variants (R5013 and 2282del4) in the filaggrin gene have been associated with atopic dermatitis (73). While the protein appears to be only weakly expressed in the human esophagus, its mRNA is strongly downregulated in patients with EoE compared to control groups and might be linked to esophageal barrier dysfunction. In a recent study of 157 control individuals and 329 patients with EoE who were analyzed for 2282del4 mutation (rs61816761), 6.1% were found to be heterozygote in the EoE group and 1.3% in the control group, demonstrating a significant association between this deletion and EoE for both genotype and allele frequency (OR 5.016 and 4.89, respectively). Interestingly, when EoE patients without any history of atopic disorders were analyzed, the 2282del4 mutation was still associated with EoE disease (42).

Besides such candidate gene approaches, a genomewide association study was conducted to unravel genetic variants associated with EoE disease (74). This study revealed a locus on the chromosome 5q22, near the TSLP gene, that was strongly associated with EoE disease (74). Polymorphisms in this locus have already been associated with other atopic diseases and peripheral blood eosinophil counts (75). In patients with EoE, the minor allele of the SNP rs3806932 correlates with decreased TSLP expression level. Moreover, the TSLP receptor (CRLF2) has the particularity to locate in the pseudoautosomal region of the X and Y chromosomes and might therefore contribute to the gender bias of the disease. Indeed, the SNP rs36133495 was found to be associated with increased EoE susceptibility in men only (37, 76).

To date, genetic variant analyses have only been conducted in a pediatric population having an early onset of the disease. Adult patients with EoE might present different gene variants. Moreover, it should be noted that all the genetic variants described above account for only a small proportion of patients with EoE. These data suggest that EoE is a polygenic disorder, with a more complex heritability than the epidemiologic data and the strong familial association would suggest. In addition, epigenetic mechanisms are highly involved in allergic diseases and a global epigenetic study might largely contribute to a better understanding of EoE pathogenesis.

Treatment for EoE in adult and pediatric patients

Indications and modalities for EoE treatment

At present, it is still debated whether the focus of EoE treatment should be directed toward a symptomatic or a histologic response, or even a combination of both parameters. Nevertheless, there are at least three good reasons to treat patients with clinically and histologically active EoE: first, *to enhance the quality of life* because dysphagia, with its ongoing risk of food impaction, has a marked negative and limiting impact on the patient's daily life (15); second, *to reduce the risk of severe esophageal injury* by preventing long-lasting food impactions, an incident occurring almost exclusively in untreated EoE (13); and third, *to prevent esophageal damage* caused by tissue remodeling owing to unbridled eosinophilic inflammation (15, 26, 30, 42, 43, 77–79).

Currently, the treatment modalities for EoE include the *3 Ds*, *d*rugs (topical corticosteroids, immunosuppressants, and biologic agents), hypo-allergic *d*iets, and finally esophageal *d*ilation (7, 8). We hereby provide further insights into the different treatment modalities for adult and for pediatric patients with EoE.

Proton pump inhibitors

In general, acid suppression using PPI should not be considered a primary therapeutic intervention for treating EoE. Instead, PPI monotherapy should be used to distinguish patients with GERD from those with EoE, and as a concurrent therapy in the case of co-existing GERD (7, 8). In addition, acid exposure is more painful in EoE subjects than in controls and, as such, isolated acid blockade may improve symptoms but not the underlying inflammatory process (80). Recently, a more complex group of patients, referred to as having 'PPI-responsive esophageal eosinophilia' (7), have been described in the adult and pediatric literature. These patients are characterized by having typical EoE symptoms, an exclusion of GERD, and a clinicopathologic response to PPI monotherapy (81, 82). It is currently unclear whether PPI-responsive esophageal eosinophilia represents a clinical subphenotype of GERD or EoE and whether the PPI response can be sustained in this group of patients.

Systemic and topical corticosteroids

In a prospective, controlled pediatric trial of oral prednisone *vs* high-dose topical fluticasone, topical fluticasone was equivalently as effective in evoking histologic and symptomatic EoE remission, as were systemic corticosteroids (83). Of note, the relapse rates after cessation of the two therapies did not differ, but systemic corticosteroids induced more side-effects. Several clinical trials in adult and pediatric EoE have demonstrated that swallowed corticosteroids (budesonide or fluticasone), deposited topically on the esophagus, are highly effective in resolving symptoms and signs of EoE (20, 79, 84, 85). While one adult study successfully used a short 2-week course of nebulized and swallowed topical budesonide (44), most other adult and pediatric studies utilize longer treatment regimens, usually 12 weeks (86, 87).

In pediatric EoE, the overall response rate to topical fluticasone administered at a dose of 440 μg twice daily via a metered dose inhaler puff and swallow was 50% (21). In addition to reducing esophageal eosinophilia, fluticasone

decreased accompanying histologic features, such as esophageal mastocytosis and basal zone hyperplasia. Interestingly, the distal esophagus tended to remain inflamed (independent of PPI use), suggesting potential incomplete drug deposition in the lower esophagus (21). Children who are young or who have developmental delay are often unable to correctly utilize an inhaler device and to adapt an appropriate swallow technique. A randomized placebo controlled trial of oral viscous budesonide (OVB, budesonide mixed with sucralose and swallowed daily at bedtime) documented significant efficacy of OVB as compared with PPI monotherapy, with an overall histologic response rate to OVB of 87% (84). One adult study using large particle nebulized, swallowed budesonide reported a similarly high success rate of 72% (44). A single case report has also documented response to OVB after fluticasone failure (88).

Adult patients can be treated with a maintenance regimen with a lower dose of topical corticosteroids. Swallowed budesonide 0.25 mg twice daily for 50 weeks was effective in keeping 50% of patients with EoE in histologic remission (89). Being a chronic disease, EoE generally recurs within a few weeks after topical corticosteroids are discontinued (21, 83, 89). The optimal maintenance regimen in pediatric EoE has not been determined (7, 8), and no studies have been published that evaluate pediatric maintenance therapies.

Leukotriene inhibitors

In an open-labeled study, Attwood and colleagues showed that montelukast, a leukotriene receptor antagonist, is able to induce symptomatic relief at high dosages, up to 100 mg daily. However, its use has not been shown to have any effect on esophageal eosinophilia (90). Unfortunately, this symptomatic relief could recently not be confirmed in a prospective study (91). The use of leukotriene inhibitors is therefore not recommended in the treatment of either adult or pediatric EoE (7, 8).

Biologic agents and immunosuppressants

Mepolizumab, a humanized anti-IL-5 antibody, led to a significant reduction of esophageal eosinophils in adult patients with EoE. However, clinical improvement was minimal (43). Two humanized monoclonal anti-IL-5 antibodies have been used in randomized pediatric EoE clinical trials. Mepolizumab was used in a parallel group, randomized trial of three active doses for 12 weeks. There was a substantial decrease in tissue eosinophilia, but only 9% of patients met the primary outcome variable of complete histologic resolution (92). Comparable with adults, the effect on symptoms was not significant.

EoE treatment with the anti-TNF antibody infliximab has not been proven to be effective in reducing eosinophilic tissue infiltration or improving symptoms (93), despite the fact that in active EoE, the squamous epithelium expresses high amounts of TNF-α (19). One pilot study has demonstrated that azathioprine or 6-mercaptopurine treatment has been effective in inducing and maintaining a remission in three corticosteroid-refractory EoE patients (94).

Elimination diets

A landmark study performed by Kelly and Sampson in 1995 demonstrated that children with esophageal eosinophilia who did not respond histologically or symptomatically to acid blockade responded to elemental formula (5). This constituted the first documentation of the potential role of food allergy in pediatric EoE. Since then, a number of independent investigators have demonstrated that amino acid–based formulas are highly effective (often >96% response) in EoE (95, 96). As elemental formulas are effective even in nonallergic inflammatory processes such as Crohn's disease, it is possible that the anti-inflammatory effect of amino acid–based diets extends beyond that of antigen elimination.

Children with EoE tend to have multiple food sensitizations with serum or skin prick IgE testing (66). However, a highly accurate predictive test for food triggers in EoE remains a pressing research need. Atopy patch testing and skin prick testing have been combined in order to target the elimination of foods. By combining skin prick and patch testing, Spergel and co-workers have demonstrated positive and negative predictive values up to 50–92% and 41–100%, respectively, for various foods (97). However, the large variability in predictive values using these testing methodologies underscores the importance for standardizing and validating tests for food allergies in EoE.

An empiric diet that eliminates common allergenic food antigens (milk, egg, soy, wheat, peanuts, tree nuts, fish, and shellfish) successfully eradicates histologic disease and symptoms in 74% of pediatric patients with EoE (50). The re-addition of milk is the most common cause of EoE recrudescence, followed by wheat, egg, and soy (52). In children, milk was 18 times more likely to re-instigate EoE as was other food. Published trials of food elimination in adults are pending, and the use of dietary therapy in adults requires further evaluation.

Esophageal dilation

Esophageal dilation may lead to long-lasting symptom improvement in patients who do not adequately respond to medical therapy and mainly present with a functional narrowing of the esophagus (98). However, dilation has no effect on the eosinophilic inflammation (98). Two recently published large series have demonstrated that esophageal dilation can be regarded as safe if performed carefully and by flexible endoscopy (98, 99). Dilation in the absence of other therapies is not utilized in pediatric EoE.

Pediatric and adult EoE, one single entity?

The preceding sections of this review highlighted important similarities and differences between adult and pediatric EoE. We now pose the crucial question as to whether adult and pediatric EoE are manifestations of a single entity or, in fact, two distinct diseases.

The first case reports and case series identified EoE as a distinct entity in adults (3, 4, 100, 101). Ironically, the first,

Table 3 Distinction between pediatric and adult eosinophilic esophagitis (EoE)

	Adult EoE	Pediatric EoE
Differences		
Clinical presentation	Dysphagia and food impaction	Nausea, anorexia, chest pain, abdominal pain, and refractory reflux
Diagnostic delay	Long	Short
Allergic predisposition	Airway allergy predominant (typically preceding EoE)	Food allergy predominant
Endoscopy	Esophageal rings, strictures	Mucosal pallor (edema), linear furrows, exudates
Response to elimination diet	Clinical efficacy currently not demonstrated	Clinical efficacy proven
Similarities		
Demographics	Male predominance Caucasian predominance High prevalence of atopy	
Laboratory tests	Elevation in serum total IgE and peripheral eosinophils in subsets of patients	
Genetics	Characterized in children; ongoing studies in adults	
Histopathology	Eosinophil-predominant inflammation and tissue injury, fibrosis	
Inflammatory/immune biomarkers	Increased tissue expression of T cells, mast cells, IL-5, TNF-α, TGF-β1, IL-13, eotaxin-3, extracellular matrix protein deposition	
Treatment	High response to topical steroids	

large cohort studies describing a dramatic rise in the prevalence of EoE originated from pediatric rather than adult medical centers (5, 6, 96, 102, 103). This description led many to believe that EoE was predominantly a childhood condition. Over the past decade, however, a growing number of reports from adult centers have recognized EoE in large cohorts (15, 24, 40, 104, 105). While most commonly seen in 30- to 40-year-old adults, the disease has even been diagnosed in octogenarians (11). While the majority of adult patients have had symptoms for several years prior to an established diagnosis of EoE, symptom onset is common in adulthood rather than childhood, arguing for an acquired rather than congenital condition (7, 8).

The majority of evidence supports a common pathogenesis for EoE in adults and children. There exist far more similarities than differences between these groups (Table 3). Demographics, including ethnicity, male predominance, family history, and atopy, are equivalent, regardless of the age at presentation. Evidence for greater importance of aeroallergen activation in adults than in children has been limited and indirect. Histologic, biomarker, and genetic studies have demonstrated a similar pattern of inflammation, lamina propria fibrosis, and genetic abnormalities. Treatment response rates to corticosteroids and hypo-allergic diets are nearly identical in children and adults.

Limited, but important, phenotypic features distinguish pediatric from adult manifestations of EoE. Pediatric presentations include a more heterogeneous spectrum of symptoms, including abdominal pain, nausea, vomiting, anorexia, and failure to thrive (7, 8). On the other hand, the clinical presentation in adults with EoE is dominated by dysphagia (7, 8). Dysphagia, while identified in pediatric series, is more common in older children and adolescents (3, 13). Food impaction is relatively uncommon in pediatric EoE but a characteristic feature in adult EoE (13). Some of these differences in symptom presentation may relate to difficulties in the ability of young children to report symptoms such as dysphagia. The symptom profile of EoE in children is similar to GERD with the exception of a greater degree of dysphagia and anorexia in EoE (106). Based on retrospective data, the endoscopic features of esophageal rings, strictures, and narrow caliber esophagus are found in a significantly greater proportion of adults than children with EoE (7, 8), but perhaps these indicate longer-standing disease and have just not yet manifest in children.

The major finding distinguishing pediatric and adult EoE relates to esophageal mural remodeling that clinically manifests as strictures and narrow caliber. Whether this difference is related to the age at presentation or duration of disease is unclear. The delayed disease identification may account for progressive tissue remodeling, leading to esophageal strictures. As mural remodeling occurs predominantly in adult patients with EoE, esophageal dilation is indicated in this patient group.

Several unanswered questions remain regarding the characterization of EoE in children and adults. A fundamental concern is whether untreated esophageal, eosinophilic inflammation in children will inevitably progress to esophageal strictures. Furthermore, the ability of chronic medical or dietary therapy to avert such progression is yet to be proven. Subpopulations of patients with food allergy, eczema, and asthma improve or resolve during the transition from childhood to adulthood, but the mechanisms are not known. Finally, genetic studies will substantiate the proposed concept of a shared etiopathogenesis between EoE in children and adults.

Conflict of interest

The authors disclose no relevant conflict of interest.

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